UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,407	10/24/2005	Osamu Okuda	053466-0409	4578

22428 7590 06/03/2008

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
06/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,407	OKUDA ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,55-59,61-71,73,74 and 76-83* is/are pending in the application.

4a) Of the above claim(s) *1-27,57 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-56, 58, 61-71, 73, 74, 76-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 60, 72, 75, have been canceled in the amendment filed 4/18/08 and claims 28-54 have been canceled previously. Amended claims 55-56, 58, 68, 69, 73, 76, 79-80 (4/18/08), previously presented claims 61-67, 70, 71, 74, 77-78, and new claims 81-83 (4/18/08) are under consideration by the Examiner.

2. Receipt of applicant's arguments and amendments filed on 4/18/2008 is acknowledged.

3. The following previous rejections and objections are withdrawn in light of applicants amendments filed on 4/18/2008:

(i) the rejection of claims 64-65, under 35 U.S.C. 112, first paragraph for deposit of biological material;

(ii) the rejection of claims 55-56, 58, 60-80, under 35 U.S.C. 112, second paragraph.

Applicant's arguments with respect to claims 55-56, 58, 61-71, 73-74, 76-83, have been considered but are moot in view of the new ground(s) of rejection;

(iii) the rejection of claims 55, 56, 68, under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,210,075 ('075 patent);

(iv) the rejection of claims 55, 56, under 35 U.S.C. 102(b) as being anticipated by WO 97/10338 (1997);

(v) the rejection of claims 55, 56, under 35 U.S.C. 102(b) as being anticipated by WO 99/64070 (1999);

(vi) the rejection of claims 55, 56, 58, 60, 61, 68, under 35 U.S.C. 102(b) as being anticipated by Choy et al (2002).

4. Applicant's arguments filed on 4/18/08 have been fully considered and were persuasive in part. The issues remaining and new issues are stated below.

Claim rejections-35 USC § 112, first paragraph, scope of enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-56, 58, 61-71, 73-74, 76-83, are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for a method for treating rheumatoid arthritis comprising administering an IL-6 receptor antibody and an immunosuppressant, wherein the antibody used is a monoclonal antibody PM-1 or MR16-1 or a humanized antibody to human IL-6 receptor, MRA, does not reasonably provide enablement for a method for treating an IL-6 related disease, comprising administering an IL-6 antagonist and an immunosuppressant to a patient requiring such a treatment or a method for the effect enhancement on the use of an IL-6 antagonist for the treatment of IL-6 related diseases, comprising administering immunosuppressants and an IL-6 antagonist to a patient requiring such a treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 4-7 of the previous Office action of 10/19/2007.

Applicants argue that in the interest of expediting prosecution, and without acquiescing to the Office's rejection, applicants amended the claims to refer to an anti-IL-6 receptor antibody which inhibits binding of IL-6 to the IL-6 receptor by binding to the IL-6 receptor to block signaling of IL-6 biological activity into cells instead of an IL-6 antagonist, suitable antibodies for use in the present invention operate by this mechanism and ultimately result in inhibition of IL-6 biological activity and that exemplary antibodies include PM-1, MR16-1 and MRA, but one of skill in the art would know how to make and use other anti-IL-6 receptor antibodies that inhibit biological activity by binding to the IL-6 receptor. However, contrary to Applicants arguments, it would require undue experimentation to determine which anti-IL-6 receptor antibodies to be administered in the claimed method would be encompassed by the scope of the claims. The disclosure of the three IL-6 receptor antibodies, is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims, which encompass every and all IL-6 receptor antibodies.

Furthermore, the amount of embodiments corresponding to the desirable compositions to be used in the claimed method, may be innumerable, and the enabled embodiments amount to only three. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe treatment of a disease other than rheumatoid arthritis by administering PM-1, MR16-1 and MRA antibodies, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. It is suggested that by employing conventional claim language, the claims be amended to include the specific antibodies supported by the instant specification in the claimed method.

In addition, the issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and In re Wands, 8USPQ2d, 1400 (CAFC 1988).

If Applicants will kindly review page 1404 of In re Wands, they will find that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. Applicants arguments that the standard is that of testing to see which anti-IL-6 receptor antibody inhibits biological activity by binding to the IL-6 receptor and to be used in the claimed method is a position that has been routinely dismissed by the courts, as shown by the decisions cited above.

Further, In re Wands determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally-occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to using naturally-occurring compounds in the claimed method. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive

contribution on the part of a practitioner which would involve the determination of which IL-6 receptor antibodies inhibit biological activity by binding to the IL-6 receptor. It is this additional characterization that is required by the instant claims that constitutes undue experimentation.

Claim rejections-35 U.S.C. 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 55-56, 58, 61-71, 73-74, 76-83, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 is vague and indefinite for several reasons.

Claim 55, is vague and indefinite because it fails to recite that an effective amount of the anti-IL-6 receptor antibody is administered to treat rheumatoid arthritis.

Claim 55, lines 3-4, are vague and indefinite because it recites that the IL-6 receptor antibody blocks signaling of IL-6 biological activity into cells. This recitation is incorrect because the IL-6 receptor antibody blocks binding of IL-6 to its receptor and therefore signaling via the IL-6 receptor is blocked, not signaling via IL-6.

Claim 56, recites the limitation "IL-6 related disease" in line 6. There is insufficient antecedent basis for this limitation in the claim (claim 56, line 4, recites “IL-6 related diseases”).

Claim 56, line 3, is vague and indefinite because it recites that the IL-6 receptor antibody blocks signaling of IL-6 biological activity into cells. This recitation is incorrect because the IL-

6 receptor antibody blocks binding of IL-6 to its receptor and therefore signaling via the IL-6 receptor is blocked, not signaling via IL-6.

Claim 58, lines 3-4, are vague and indefinite because it recites that the IL-6 receptor antibody blocks signaling of IL-6 biological activity into cells. This recitation is incorrect because the IL-6 receptor antibody blocks binding of IL-6 to its receptor and therefore signaling via the IL-6 receptor is blocked, not signaling via IL-6.

Claim 58, line 4, is vague and indefinite because it is unclear what the upper limit on the dose is because the claim recites "dose of 4 mg/kg/4 weeks or more".

Claims 63, 66-67, are rejected as vague and indefinite because they are dependent on canceled claim 60.

Claim 68, is redundant because it recites that the IL-6 related disease is "rheumatoid arthritis" and therefore the claim fails to further limit claim 55.

Claims 81-83, are rejected as vague and indefinite because they are improper Markush claims. The claims fail to recite ".....selected from the group consisting of PM-1, MR16-1, and MRA".

Claims 61-62, 64-65, 69-71, 73-74, 76-80, are rejected as vague and indefinite insofar as they depend on the above rejected claims for their limitations.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7a. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,888,510 ('510 patent).

This rejection is maintained for reasons of record set forth at page 9 of the previous Office action of 10/19/2007.

Applicants argue that claim 58 recites a limitation on the dosage and time interval of administration, i.e., 4 mg/kg/4 weeks or more and that the '510 patent fails to describe the claimed administration amount and the administration interval of the present invention and therefore claim 58 is not anticipated by the cited art. However, contrary to Applicants arguments, claim 58 is unclear because it recites "dose of 4 mg/kg/4 weeks or more". Therefore, the prior art anticipates claim 58.

7b. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Nishimoto et al (2002).

This rejection is maintained for reasons of record set forth at page 9 of the previous Office action of 10/19/2007.

Applicants argue that claim 58 recites a limitation on the dosage and time interval of administration, i.e., 4 mg/kg/4 weeks or more and that the Nishimoto reference fails to describe the claimed administration amount and the administration interval of the present invention and therefore claim 58 is not anticipated by the cited art. However, contrary to Applicants

arguments, claim 58 is unclear because it recites "dose of 4 mg/kg/4 weeks or more". Therefore, the prior art anticipates claim 58.

7c. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by EP 1074268 (2001).

This rejection is maintained for reasons of record set forth at pages 9-10 of the previous Office action of 10/19/2007.

Applicants argue that claim 58 recites a limitation on the dosage and time interval of administration, i.e., 4 mg/kg/4 weeks or more and that the EP 107268 reference fails to describe the claimed administration amount and the administration interval of the present invention and therefore claim 58 is not anticipated by the cited art. However, contrary to Applicants arguments, claim 58 is unclear because it recites "dose of 4 mg/kg/4 weeks or more". Therefore, the prior art anticipates claim 58.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8a. Claims 55, 56, 58, 61, 62, 63, 68-71, 73-74, 76-80, are rejected under 35 U.S.C. 103(a) as unpatentable over Choy et al (2002).

This rejection is maintained for reasons of record set forth at pages 11-12 of the previous Office action of 10/19/2007.

Applicants argue that Choy describes a combined use of an anti-IL-6 receptor antibody and prednisolone, and there would be no reasonable expectation of success to replace prednisolone with immunosuppressants. Applicants also argue that the Choy reference does not motivate a person with ordinary skill in the art to replace prednisolone with immunosuppressants for the following reasons.

(1) The Choy reference refers to "Concomitant oral steroid treatment was permitted if the dose was ....." The phrase "was permitted" means that Choy did not positively use prednisolone.

(2) The presently claimed invention is directed to a combined use of an anti-IL-6 receptor antibody and MTX, which is an immunosuppressant, while Choy on page 3144, lower right column, beginning at line 11 describes the use of parenteral and/or intraarticular steroids,

immunosuppressants, investigational drugs and oral anticoagulant drugs, and specifically states that such drugs within 4 weeks before administration of the study medication was not permitted.

(3) Choy does not suggest that combined use of an anti-IL-6 receptor antibody provides a better therapeutic effect in comparison with the use of an anti-IL-6 receptor antibody alone and thus, a person of ordinary skill in the art would be lead to believe, from the teachings of Choy, that the prednisolone does not provide a substantial effect.

However, contrary to Applicants arguments, this rejection is a 35 USC 103(b) rejection not a 35USC 102 rejection. If the Choy reference disclosed administration of an anti-IL-6 receptor antibody and MTX, this would be a 35 USC 102(b) rejection rather than a 35 USC 103 rejection. The reference suggests the administration of an anti-IL-6 receptor antibody and an immunosuppressant. Furthermore, claim 58 is unclear because it recites the limitation "dose of 4 mg/kg/4 weeks or more". Since, there is no upper limit on the dosage or time frame, the reference renders obvious the claimed invention. Furthermore, the reference does not have to specifically recite that the combined use of the anti-IL-6 receptor antibody and the prednisolone provides a better therapeutic effect in comparison with the use of anti-IL-6 receptor antibody alone. The reference suggests the combined administration of the immunosuppressant with the anti-IL-6 receptor antibody. Thus the artisan would have expected equal success using methotrexate. Furthermore, one of skill in the art would have been motivated to adjust the dosage of the IL-6R antibody to determine the dosage which has the maximum effect at the minimum dosage for highest efficiency. As the administration schedule of the anti IL6-R antibody and the immuno-suppressant does not have any surprising effect, the subject-matter of claims 55, 56, 58, 61, 62, 63, 68-71, 73-74, 76-80, is rendered obvious by the reference.

8b. 55, 56, 58, 61, 62, 63, 66, 68-71, 73-74, 76-80, are rejected under 35 U.S.C. 103(a) as unpatentable over Choy et al (2002) in view in of Queen et al. (U.S. Patent No. 5,530,101).

This rejection is maintained for reasons of record set forth at pages 12-13 of the previous Office action of 10/19/2007.

Applicants argue that for the reasons described in the arguments against the Choy et al patent as a 35 USC 103 reference, the teachings of Choy in combination with the Queen et al. (U.S. Patent No. 5,530,101) reference does not render obvious the claimed invention. However, contrary to Applicants arguments, for the reasons set forth above in paragraph 8a, the subject-matter of claims 55, 56, 58, 61, 62, 63, 68-71, 73-74, 76-80, is rendered obvious by Choy et al (2002) in view in of Queen et al. (U.S. Patent No. 5,530,101).

Conclusion

No claim is allowed.

Claims 55-56, 58, 61-71, 73-74, 76-83, are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
Primary Examiner
Art Unit 1646